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Using a Bayesian change-point statistical model with autoregressive terms to study the monthly number of dispensed asthma medications by public health services

J.A M. de Queiroz[1,2], D.C. Aragon[3], L.M. de Mello[4], I.T.S. Previdelli[2] and E.Z. Martinez[4,*]

Abstract

In this paper, it is proposed a Bayesian analysis of a time series in the presence of a random change-point and autoregressive terms. The development of this model was motivated by a data set related to the monthly number of asthma medications dispensed by the public health services of Ribeirão Preto, Southeast Brazil, from 1999 to 2011. A pronounced increase trend has been observed from 1999 to a specific change-point, with a posterior decrease until the end of the series. In order to obtain estimates for the parameters of interest, a Bayesian Markov Chain Monte Carlo (MCMC) simulation procedure using the Gibbs sampler algorithm was developed. The Bayesian model with autoregressive terms of order 1 fits well to the data, allowing to estimate the change-point at July 2007, and probably reflecting the results of the new health policies and previously adopted programs directed toward patients with asthma. The results imply that the present model is useful to analyse the monthly number of dispensed asthma medications and it can be used to describe a broad range of epidemiological time series data where a change-point is present.

MSC: 62P10, 62F15, 62M10, 37M10.

Keywords: Time series, regression models, Bayesian methods, change-point model, epidemiological data.

*e-mail: edson@fmrp.usp.br

[1] Instituto Federal de Educação, Ciência e Tecnologia do Paraná (IFPR), Jacarezinho, Brazil

[2] Master Program in Biostatistics, Department of Statistics, State University of Maringá (UEM), Maringá, PR, Brazil

[3] Department of Pediatrics, Ribeirão Preto Medical School, University of São Paulo (USP), Ribeirão Preto, SP, Brazil

[4] Department of Social Medicine, Ribeirão Preto Medical School, University of São Paulo (USP), Ribeirão Preto, SP, Brazil.

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1. Introduction

In many situations, epidemiological data come in the form of time series. Disease notifications, hospitalizations due to a specific disease and mortality rates over a given time interval are examples of variables which can be studied as time series. Statistical models are useful to describe patterns of these series, such as temporal trends and seasonal fluctuations. These models can be also used to predict future observations after observing a series of longitudinal data, thus supplying information to aid in the surveillance and management of events of public health interest.

Change-point models (Jensen and Lautkebohmert, 2007; Lee, 2010) have been increasingly used in a broad spectrum of applications, such as in econometrics (Hackl, 2012), medicine (Ghosh and Vaida, 2007) and environmental studies (Achcar et al., 2010; Achcar, Rodrigues and Tzintzun, 2011). These models are statistical tools used in practical problems where a random variable indexed by time has modified their behaviour at one or more time instants. Thus, these models are useful when the interest of the analyst lies in determining whether the observed time series is homogeneous over the time interval. As an example, Achcar et al. (2008) considered a change-point analysis for the incidence of tuberculosis cases in New York City from 1970 to 2000, when the number of cases of the disease presented three trends. In the first period of time, the trend of declining incidence was probably associated with good control programs. In the second period, there were increasing incidence rates, and in the third period there was a new trend of declining rates. Modern Bayesian methods of inference by using Markov Chain Monte Carlo (MCMC) techniques have been used to fit time series data in the presence of one or more change-points (Achcar and Loibel, 1998; Barry and Hartigan, 1993; Carlin, Gelfand and Smith, 1992; Dey and Purkayastha, 1997; Lavielle and Lebarbier, 2001), including multiple change-point models where the number of change-points is unknown (Chib, 1998; Fearnhead, 2006).

The present article introduces a single Bayesian model for change-point detection including autoregressive terms to be applied to the monthly number of asthma medications dispensed by the public health services of Ribeirão Preto, Southeastern Brazil. Climatic variables are included as independent variables.

2. Methods

2.1. Field of study and dataset

The present study is part of a larger research on dispensation of medications to treat pulmonary diseases in the public health services of Ribeirão Preto, a city located in the northwest region of the State of São Paulo, Brazil. Ribeirão Preto is ranked the eighth largest city in the State of São Paulo, with about 600 thousand inhabitants (IBGE census data, available from www.censo2010.ibge.gov.br/sinopse/). The city belongs to the health coverage area of the XIII Regional Health Department of the Health Secretariat

of the State of São Paulo, being considered a regional health care centre reference for interventions of medium and high complexity and attending more than 1.2 million people, of which approximately 62% depend exclusively on the Brazilian National Health System (SUS) (Bittar, Mendes and Magalhães, 2011). The public healthcare network in Ribeirão Preto is composed by municipal, state and philanthropic services, involving 36 pharmacies providing pharmaceutical care according to the National Drug Policy guidelines (GM Ordinance number 3916 of November 30th, 1998) and currently offering to the population over 260 medications indicated for the treatment of various diseases, including asthma.

Table 1: *Monthly data on the number of dispensed medications (salbutamol sulfate tablets of 2 mg) in Ribeirão Preto, Brazil, from February 1999 to December 2011.*

Year	Jan.	Feb.	Mar.	Apr.	May.	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
1999		2,376	2,900	1,699	2,066	4,329	5,486	5,651	7,732	5,505	4,267	3,843
2000	6,855	7,809	7,659	6,386	6,822	8,297	5,936	8,255	6,171	7,119	4,980	7,523
2001	9,563	9,269	9,605	10,150	11,867	10,482	11,718	12,412	9,183	13,667	12,046	9,150
2002	10,641	11,975	10,651	6,089	13,843	15,336	16,418	15,401	12,518	12,960	11,295	13,100
2003	11,756	5,043	2,057	9,131	13,654	12,785	15,071	10,549	11,633	9,085	12,884	11,218
2004	10,477	12,671	18,303	17,445	15,606	15,011	19,448	17,124	15,132	13,218	17,054	14,596
2005	14,433	12,569	17,053	16,110	18,346	19,218	18,847	19,209	15,435	18,274	17,313	18,392
2006	13,411	12,675	18,597	16,258	20,357	20,457	16,339	18,552	16,910	20,617	19,634	23,567
2007	21,981	22,981	25,914	21,607	30,083	19,008	23,103	21,893	16,974	20,066	17,606	15,846
2008	18,134	18,578	18,306	17,982	21,032	19,222	19,274	15,841	13,864	14,600	13,431	12,865
2009	11,722	10,862	14,184	13,414	15,257	16,914	13,906	14,752	14,762	14,305	12,590	14,843
2010	11,876	12,284	14,468	13,505	13,765	11,929	4,313	10,475	11,644	11,837	9,949	10,040
2011	9,328	9,095	8,998	7,987	8,161	9,278	7,343	7,672	6,082	5,678	6,141	4,951

Data on the number of dispensed medications were provided by the HygiaWeb Information System, a health information system which has been used by the Municipal Health Secretariat of Ribeirão Preto since 1992. This system enables to record information on health services in the entire municipal public healthcare network. In 1998, the implementation of a medication management module in the HygiaWeb System enabled the recording of data on dispensation of medications and pharmaceutical care. Therefore, it has been possible to retrieve secondary information about the dispensation of the main medications for asthma treatment since 1999, covering the whole city. For the purposes of the present study, data on only one drug used to alleviate the symptoms of asthma have been considered for developing the statistical model, namely, salbutamol sulfate tablets of 2 mg. Full data on the number of dispensed medications, from February 1999 to December 2011, are listed in Table 1. In addition, data on temperature and precipitation in the city of Ribeirão Preto were obtained from the Integrated Agrometeorological Information Center of the Agronomic Institute (CIIAGRO, Centro Integrado de Informações Agrometeorológicas do Instituto Agronômico).

The local Research Ethics Committee has approved the present study (CEP/CSE/FMRP/USP, protocol number 453) and the permission to access and use the records from

the HygiaWeb System was granted by the local representative of the Health Department (document 248/11-GS RAS/ras).

2.2. Statistical model

Let y_t be the number of dispensed medications at the month t, $t = 1,\ldots,n$, where n is the number of months in the time series. The proposed model is given in a general form by

$$y_t = \alpha + g_1 I_{[1,\theta]}(t) + g_2 I_{(\theta,n]}(t) + S_t + \varepsilon_t,$$

where

$$g_k(t) = \beta_k (t-\theta) + \sum_{r=1}^{R} \psi_{kr} (x_{rt} - \overline{x}_r) + \sum_{j=1}^{p} \gamma_{kj} (y_{t-j} - \overline{y}), \;\; k = 1,2,$$

α is an intercept term, $I_{\{A\}}(t)$ denotes an indicator function such that $I_{\{A\}}(t) = 1$ if $t \in \{A\}$, and 0 otherwise, θ is the change-point to be estimated such that θ is an integer number in the interval $[1,n]$, $x_{1t}, x_{2t}, \ldots, x_{Rt}$ are observations of R covariates at the month t, $\overline{x}_r$ denotes the mean of $x_{r1},\ldots,x_{rn}$, $r = 1,\ldots,R$, ψ_{1r} and ψ_{2r} are the effects of the covariate x_{rt} on y_t before and after θ, respectively, $\overline{y}$ denotes the mean of $y_1,\ldots,y_n$, the terms $\gamma_{11},\ldots,\gamma_{1p},\gamma_{21},\ldots,\gamma_{2p}$, are autoregressive parameters of order p to be estimated and the random error terms are represented by ε_t. In addition,

$$S_t = \eta_1 \sin\left(\frac{2\pi t}{12}\right) + \eta_2 \cos\left(\frac{2\pi t}{12}\right)$$

is a monthly periodic function for estimating seasonal patterns, where η_1 and η_2 are real numbers. By using this model, it is assumed that the terms ε_t, $t = 1,\ldots,n$, are independent and follow the normal distribution with mean 0 and variance depending on the change-point θ, or say,

$$\varepsilon_t \sim N\left(0, \sigma_1^2 I_{[1,\theta]}(t) + \sigma_2^2 I_{(\theta,n]}(t)\right).$$

Thus, σ_1^2 and σ_2^2 are the variances of ε_t before and after the change-point, respectively. This model formulation corresponds to the following likelihood function:

$$f(\mathbf{y}|\theta,\boldsymbol{\xi}) = \prod_{t=1}^{n} (2\pi\lambda_t)^{-\frac{1}{2}} \exp\left[-\sum_{t=1}^{n} \frac{(y_t - \mu_t)^2}{2\lambda_t}\right],$$

where

$$\lambda_t = \sigma_1^2 I_{[1,\theta]}(t) + \sigma_2^2 I_{(\theta,n]}(t), \tag{1}$$

$$\mu_t = \alpha + g_1 I_{[1,\theta]}(t) + g_2 I_{(\theta,n]}(t) + S_t, \tag{2}$$

$\mathbf{y} = (y_1, y_2, \ldots, y_n)^\intercal$ and $\boldsymbol{\xi} = (\alpha, \beta_1, \beta_2, \gamma_{1,1}, \ldots, \gamma_{1,p}, \gamma_{2,1}, \ldots, \gamma_{2,p}, \psi_{1,1}, \ldots, \psi_{1,R}, \psi_{2,1}, \ldots, \psi_{2,R}, \sigma_1^2, \sigma_2^2, \eta_1, \eta_2)^\intercal$ is the vector of parameters. By definition, $f(\mathbf{y}|\theta,\boldsymbol{\xi})$ denotes the joint probability density function of the sample $Y = (Y_1, Y_2, \ldots, Y_n)$. In the Bayesian analysis, it is assumed that the parameters of the vector $\boldsymbol{\xi}$ and θ have distributions based on previous knowledge (the prior distributions), which are updated by using the data (represented by $f(\mathbf{y}|\theta,\boldsymbol{\xi})$) to produce the posterior distributions. This is formalized by the Bayes' theorem, given by $f(\theta,\boldsymbol{\xi}|\mathbf{y}) \propto f(\mathbf{y}|\theta,\boldsymbol{\xi})\, p(\theta,\boldsymbol{\xi})$, where $p(\theta,\boldsymbol{\xi})$ is the joint prior distribution and $f(\theta,\boldsymbol{\xi}|\mathbf{y})$ is the joint posterior distribution. The prior distributions can be "non-informative", with little effect on the posterior distribution. Thus, the following prior distributions for the parameters of the vector $\boldsymbol{\xi}$ are considered: $\alpha \sim N(0, c_1)$, $\beta_1 \sim N(0, c_2)$, $\beta_2 \sim N(0, c_3)$, $\gamma_{1,j} \sim N(0, c_{4,j})$, $\gamma_{2,j} \sim N(0, c_{5,j})$, $j = 1, \ldots, p$, $\eta_1 \sim N(0, c_6)$, $\eta_2 \sim N(0, c_7)$, $\psi_{1,r} \sim N(0, c_{8,r})$, $\psi_{2,r} \sim N(0, c_{9,r})$, $r = 1, \ldots, R$, $\sigma_1^2 \sim IG(c_{10}, c_{11})$ and $\sigma_2^2 \sim IG(c_{12}, c_{13})$, where $c_1, \ldots, c_{13}$ are known values for the hyperparameters of the prior distributions, $N(0, c)$ denotes a normal distribution with mean 0 and variance c, and $IG(h_1, h_2)$ denotes an inverse gamma distribution with mean $h_2/(h_1 - 1)$ and variance $h_2^2/[(h_1 - 1)^2(h_1 - 2)]$. Large values of $c_1, \ldots, c_{13}$ yield non-informative prior distributions for their respective parameters. It is further assumed prior independence among these parameters. In addition, it is assumed a categorical prior distribution for the change-point θ such that the prior probabilities of the values $1, 2, \ldots, n$ are assumed to be equal to $1/n$.

Alternatively, it can be considered that the terms ε_t follow a non-standardized Student's t-distribution with υ degrees of freedom, a location parameter μ_t, a scale parameter λ_t and variance $\lambda_t^2 \upsilon (\upsilon - 2)^{-1}$ for $\upsilon > 2$. In this case, the model formulation corresponds to the following likelihood function:

$$f(\mathbf{y}|\theta, \upsilon, \boldsymbol{\xi}) = \prod_{t=1}^{n} \left\{ \frac{\Gamma\left(\frac{\upsilon+1}{2}\right)}{\Gamma\left(\frac{\upsilon}{2}\right) \lambda_t \sqrt{\pi \upsilon}} \left[1 + \frac{1}{\upsilon} \left(\frac{y_t - \mu_t}{\lambda_t} \right)^2 \right]^{-\frac{\upsilon}{2}} \right\},$$

where $\Gamma(\cdot)$ is the gamma function, and λ_t and μ_t are given by (1) and (2), respectively. For the Bayesian analysis, one can consider the same prior distributions assumed for the previous model and a continuous uniform prior distribution for υ, or say, $\upsilon \sim U(2, c_\upsilon)$, where c_υ is a known hyperparameter ($c_\upsilon > 2$). In order to perform a brief sensitivity analysis, we have also considered fixed values for υ.

A Bayesian Markov Chain Monte Carlo (MCMC) procedure using the Gibbs sampler algorithm (Casella and George, 1992) was used to estimate the posterior distributions of the parameters of interest and variance components (Carlin and Louis, 1996). The Gibbs sampler algorithm was run for 510,000 iterations and sampled in every 10th simulation. To eliminate the effect of the initial values, the first 10,000 iterations were discarded as a "burn-in-sample". In this way, 50,000 final Gibbs samples were used for inferences. The 95% credible intervals ($95\%CI$) were obtained from the 2.5% and 97.5% percentiles of the posterior samples of the parameters. The 95% credible inter-

vals are the Bayesian equivalent of the traditional 95% confidence intervals, expressing the central 95% of the range of values that are credible for the respective estimated parameter. Usual diagnostic methods were employed to check the convergence of the MCMC calculations (Carlin and Louis, 1996). After the model fitting, the assumption of independence between the successive random error terms ε_t was graphically verified by plotting their respective autocorrelation and partial autocorrelation functions in relation to different lags. The estimation was performed by using the MCMC algorithm implemented in the freely available OpenBUGS software (Lunn et al., 2000). The OpenBUGS code used for this analysis is given in the Appendix A.

2.3. Model specifications

In the absence of covariates, three different models were fitted to the data as described below.

- **Model 1:** In this model, the autoregressive terms $\gamma_{1,1},\ldots,\gamma_{1,p},\gamma_{2,1},\ldots,\gamma_{2,p}$ were discarded, and consequently, $g_k = \beta_k(t-\theta)$, for $k = 1,2$. This model does not consider the presence of covariates, nor the monthly periodic function S_t.
- **Model 2:** This model is similar to Model 1 but it considers the autoregressive terms $\gamma_{1,1},\ldots,\gamma_{1,p},\gamma_{2,1},\ldots,\gamma_{2,p}$.
- **Model 3:** This model is similar to Model 2 but it considers the monthly periodic function S_t.

Models 1 to 3 were fitted based on the assumption that the residuals ε_t follow a normal distribution or a Student's t-distribution. In addition, Model 4 is defined as follows:

- **Model 4:** This model is similar to Model 3, but it includes an independent variable. The following variables were considered: average monthly temperature (^{o}C), maximum and minimum monthly temperature (^{o}C) and average monthly precipitation (mm). Due to its highly skewed distribution, a log transformation was applied to the measures of average monthly precipitation. These variables were selected due to their known effects on the asthma admissions in various populations (Ivey, Simeon and Monteil, 2003; Chen, Xirasagar and Lin, 2006). Under this formulation, four different models were fitted to the data, one for each independent variable, thus avoiding problems of collinearity between variables.

2.4. Model selection

The deviance information criterion (DIC) is widely used for Bayesian model comparison (Spiegelhalter et al., 2014). However, the proposed model is interpreted by the OpenBUGS as a mixture model, and this software is not able to calculate the DIC value

in this situation. Another criterion for model selection is derived from the conditional predictive ordinate (CPO) statistics (Gelfand, Dey and Chang, 1992). For the i-th observation, the CPO_i is given by

$$f\left(\mathscr{D}_i|\mathbf{y}_{[i]}\right) = \int f\left(\mathscr{D}_i|\Theta\right) f\left(\Theta|\mathscr{D}_{[i]}\right) d\Theta,$$

where Θ is the complete vector of parameters, $\mathscr{D}_i$ is each instance of all data $\mathscr{D}$, $\mathscr{D}_{[i]}$ is $\mathscr{D}$ without the current observation i and $f\left(\Theta|\mathscr{D}_i\right)$ is the posterior density of Θ given $\mathscr{D}_{[i]}$, $i = 1,\ldots,n$. Thus, the CPO statistics expresses the posterior probability of observing the value or set of values of $\mathscr{D}_i$ when the model is fitted to all data except $\mathscr{D}_i$. A MCMC approximation of CPO_i (Chen, Shao and Ibrahim, 2000) is given by

$$\widehat{CPO}_i = \left[\frac{1}{B}\sum_{b=1}^{B}\frac{1}{f\left(\mathscr{D}_i|\Theta_b\right)}\right]^{-1}$$

where B is the number of iterations during implementation of the MCMC procedure after the burn-in period and Θ_b is the vector of the samples obtained at the b-th iteration. Thus, approximate CPO statistics can be directly computed with OpenBUGS by defining nodes for $f\left(\mathscr{D}_i|\Theta_b\right)^{-1}$. Assuming approximate normality, inverse values for $\widehat{CPO}_i$ larger than 40 can be considered as possible outliers and higher than 70 as extreme values (Ntzoufras, 2009). The log pseudo marginal likelihood (LPML) is a Bayesian measure of fit or adequacy which is defined based on the CPO statistics (Geisser and Eddy, 1979). For a given model, the LPML value is given by $\widehat{LPML} = \sum_{i=1}^{n}\log\widehat{CPO}_i$.

The larger is the value of LPML, the better is the fit of the model. The corresponding pseudo Bayes' factor (PBF) comparing models m and $m\prime$ is

$$PBF_{mm'} = \exp\left(\widehat{LPML}_m - \widehat{LPML}_{m'}\right).$$

In addition, the discrepancy between the data and an estimation model can be measured by the sum of squared residuals (SSR) given by

$$SSR = \sum_{i=1}^{n}\varepsilon_i^2 = \sum_{i=1}^{n}\left(y_i - \widehat{\mu}_t\right)^2,$$

where $\widehat{\mu}_t$ is obtained by replacing the parameters in (2) by their respective estimates. For fits of different models to a given dataset, a smaller SSR value indicates a better fit to the data.

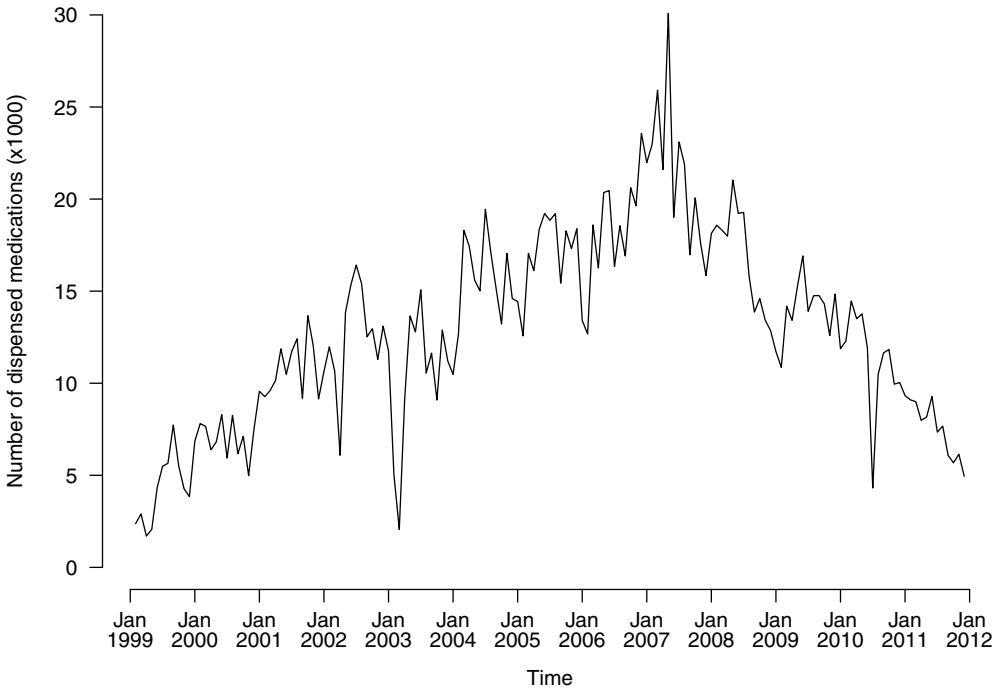

Figure 1: *Monthly number of dispensed medications (salbutamol capsule, 2mg) by the public health services of Ribeirão Preto, Brazil, from February 1999 to December 2011.*

3. Results

The graph in Figure 1 shows a time series of the number of monthly dispensations of the salbutamol from February 1999 to December 2011. This graph gives evidence of the presence of a change-point for the time series. It is observed an increase in the number of dispensations of the medication at the beginning of the considered period and a great reduction in March 2003, probably due to the short period when the drug was missing, followed by a further increase in the number of dispensations, until May, 2007. Thereafter, it is observed that the number of dispensed medications decreases until the end of the period of observation. A great reduction in the number of dispensations was also observed in July 2010. However, in the analysis of these data, only one change-point in the time series will be considered. The reductions in the number of dispensations observed in March 2003 and July 2010 will be treated as months with atypical numbers of dispensed medications, instead of instants in which the trend behaviour of the series has been modified.

In the Bayesian analysis, non-informative prior distributions were considered for all parameters of the model. In this way, it was considered that $c_1 = c_2 = c_3 = c_{4,j} = c_{5,j} = c_6 = c_7 = c_{8,r} = c_{9,r} = 10^6$, $j = 1, \ldots, p$, $r = 1, \ldots, R$, in the prior distributions for α, β_1,

β_2, $\gamma_{1,j}$, $\gamma_{2,j}$, $\psi_{1,r}$ and $\psi_{2,r}$, and $c_{10} = c_{11} = c_{12} = c_{13} = 0.1$ in the prior distributions for σ_1^2 and σ_2^2. In the case of the model with Student-t errors, it is also considered $c_\upsilon = 50$, or say, $\upsilon \sim U(2,50)$. The number of monthly dispensed medications was divided by 1,000 in order to facilitate the convergence of the computational algorithm.

Tables 2 and 3 show the results for the Models 1 to 3 obtained by using the OpenBUGS software. The results in Table 2 consider that the residuals of the models follow a normal distribution, while Table 3 shows results from models with residuals that follow a Student's t-distribution with υ degrees of freedom. In the case of the Models 2 and 3, they were fitted considering one, two or more autoregressive orders, but it was observed that models with order p equal to or greater 2 did not improve the goodness of fit. Thus, we considered $p = 1$ in all the cases.

Table 2 shows that the results of Model 3 have the lowest SSR value and the highest LPML value, suggesting that this model provides the best fit to the data among these three models. The *PBF* value comparing the Models 3 and 2 is 6.05. In all the fitted models, the estimates for β_1 are positive and the estimates for β_2 are negative, showing that the number of dispensed medications is increasing over time until the change-point θ is reached, but decreasing from this value. The 95% credible intervals for $\gamma_{1,1}$ and $\gamma_{2,1}$ do not contain the value zero, evidencing the significance of the autoregressive parameters of order $p = 1$. The results of Model 3 also show that the 95% credible interval for η_2 do not contain the value zero, suggesting the evidence of a yearly seasonal pattern in the series.

Table 2: *Results from the Bayesian change-point statistical models, with residuals following a normal distribution.*

Parameter	Model 1		Model 2		Model 3	
	Bayesian estimate	95% credible interval	Bayesian estimate	95% credible interval	Bayesian estimate	95% credible interval
α	20.80	(20.01 , 21.59)	17.67	(16.18 , 19.13)	18.11	(16.61 , 19.58)
β_1	0.166	(0.149 , 0.182)	0.094	(0.062 , 0.125)	0.104	(0.072 , 0.135)
β_2	−0.268	(−0.297 , −0.240)	−0.178	(0.230 , −0.127)	−0.191	(−0.242 , −0.141)
θ	100.5	(99.0 , 103.0)	102.3	(100.0 , 107.0)	101.9	(100.0 , 107.0)
$\gamma_{1,1}$	–	–	0.444	(0.282 , 0.607)	0.401	(0.237 , 0.564)
$\gamma_{2,1}$	–	–	0.295	(0.099 , 0.500)	0.236	(0.041 , 0.439)
σ_1^2	7.82	(5.88 , 10.36)	6.51	(4.87 , 8.65)	6.24	(4.64 , 8.29)
σ_2^2	4.09	(2.73 , 6.16)	3.57	(2.32 , 5.53)	3.40	(2.22 , 5.22)
η_1	–	–	–	–	0.464	(−0.024 , 0.954)
η_2	–	–	–	–	−0.585	(−1.107 , −0.068)
LPML	−364.8		−354.7		−352.9	
SSR	967.2		805.2		758.4	

Table 3: *Results from the Bayesian change-point statistical models, with residuals following a Student's t-distribution with υ degrees of freedom.*

Parameter	Model 1		Model 2		Model 3	
	Bayesian estimate	95% credible interval	Bayesian estimate	95% credible interval	Bayesian estimate	95% credible interval
α	20.88	(20.11 , 21.64)	17.76	(16.26 , 19.19)	18.19	(16.75 , 19.57)
β_1	0.166	(0.150 , 0.183)	0.096	(0.064 , 0.128)	0.104	(0.073 , 0.135)
β_2	-0.263	(-0.292 , -0.235)	-0.177	(-0.228 , -0.124)	-0.190	(-0.237 , -0.141)
θ	99.9	(97.0 , 102.0)	101.9	(95.0 , 107.0)	102.0	(97.0 , 106.0)
υ (df)	11.1	(3.1 , 40.6)	13.2	(3.4 , 43.8)	9.2	(2.9 , 34.7)
$\gamma_{1,1}$	–	–	0.423	(0.258 , 0.590)	0.383	(0.220 , 0.543)
$\gamma_{2,1}$	–	–	0.303	(0.104 , 0.510)	0.244	(0.063 , 0.437)
σ_1^2	5.40	(3.22 , 8.22)	4.90	(2.94 , 7.23)	4.35	(2.62 , 6.59)
σ_2^2	3.11	(1.70 , 5.16)	2.68	(1.43 , 4.56)	2.16	(1.13 , 3.76)
$\sigma_1^2\upsilon(\upsilon-2)^{-1}$	7.85	(5.27 , 12.29)	6.60	(4.53 , 9.82)	6.69	(4.38 , 10.70)
$\sigma_2^2\upsilon(\upsilon-2)^{-1}$	4.55	(2.65 , 8.00)	3.63	(2.07 , 6.49)	3.35	(1.81 , 6.20)
η_1	–	–	–	–	0.510	(0.062 , 0.951)
η_2	–	–	–	–	-0.631	(-1.091 , -0.161)
LPML	-472.8		-442.8		-465.4	
SSR	968.0		808.8		766.9	

The results in Table 3 indicate that the estimates obtained from the models with residuals following a Student's t-distribution are close to those found when considering a normal distribution (Table 2). The graphs in Figure 2 illustrate the simulated posterior Gibbs samples for the change-point in each of the three assumed models. In addition, plots of the autocorrelation function (ACF) and the partial autocorrelation function (PACF) of the residuals of the Models 1 to 3 are shown in Appendix B. The ACF and PACF of residuals of the Models 2 and 3 at different lag times were not significantly different from zero. From equation (1), the variances of ε_t before and after the change-point are given by $\sigma_1^2\upsilon(\upsilon-2)^{-1}$ and $\sigma_2^2\upsilon(\upsilon-2)^{-1}$, respectively. Estimators for these quantities are also presented in Table 3, and we can note that they are very similar to those for σ_1^2 and σ_2^2 obtained from the fit of the models based on the normal distribution (Table 2). Alternatively, we also considered models based on the Student's t-distribution with fixed values for υ ranging from 2 to 50. For each possible choice of υ, we obtained the correspondent values for LPML and SSR considering the Models 1 to 3 (results not shown in the tables). We did not find important differences when compared the LPML and SSR values obtained from models with fixed values for υ ranging from 2 to 50. However, we noted a better fit to the data (i.e. higher LPML values and lower SSR values) for values relatively higher for υ, such as $\upsilon = 100$ or $\upsilon = 200$, thus suggesting that models based on the normal distribution can be more adequate for the monthly number of dispensed medications.

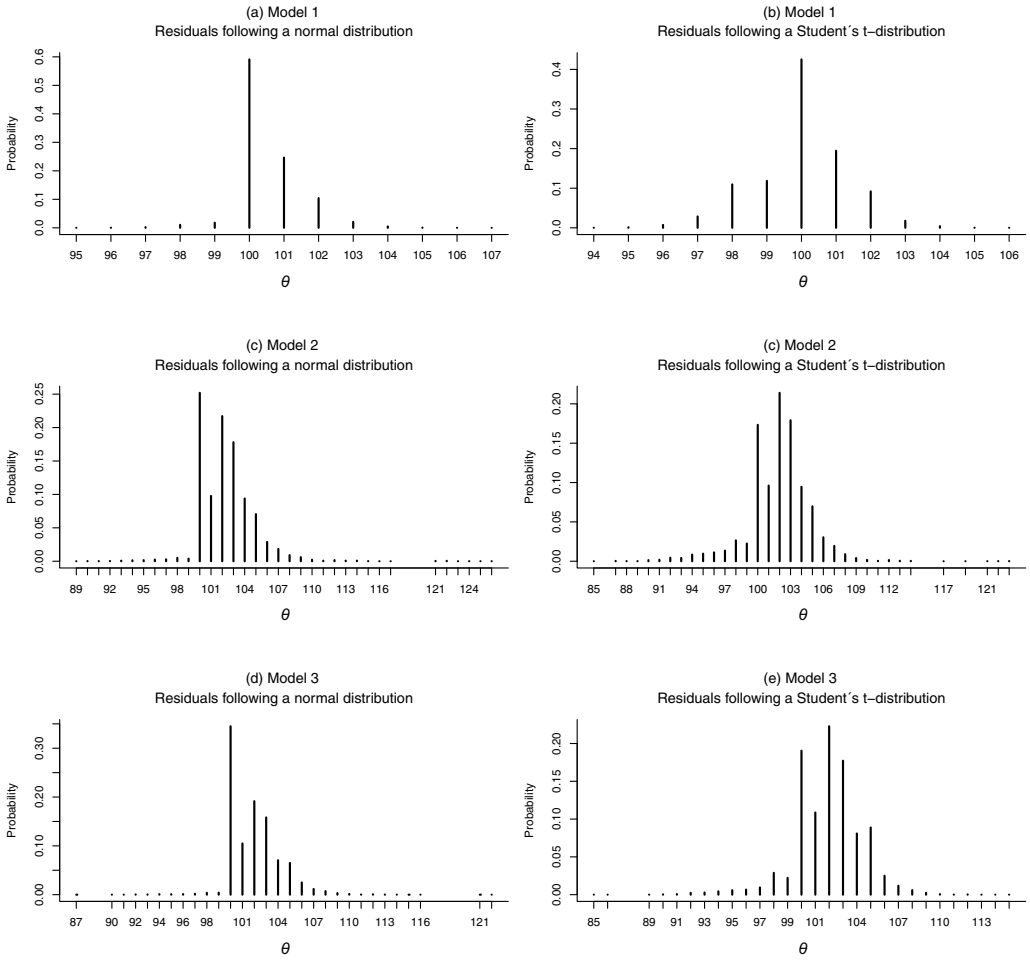

Figure 2: *Plots of the simulated posterior Gibbs samples for the change-point in each of the three assumed models.*

The upper panel of the Figure 3 shows the observed number of dispensed medications and the predicted values obtained from Model 1. Considering the results from the Model 1 with residuals that follow a normal distribution, the predicted values linearly increase up to the change-point θ estimated by $t = 100.5$ (Table 2), corresponding to the month of May, 2007, with a 95% credible interval ranging from April 2007 to August 2007. After this change-point, the predicted values linearly decrease with the coefficient β_2 estimated by -0.268. Considering the Model 1 with residuals that follow a Student's t-distribution, the change-point θ is estimated by $t = 99.9$ (Table 3). However, autocorrelation plots (not shown) for the residuals from Model 1 evidence significant serial correlation between successive values of ε_t, that is, the assumption of independence between the residuals was not attained. Therefore, Model 1 is useful to describe the linear trend of the time series before and after the change-point, but inferences for the

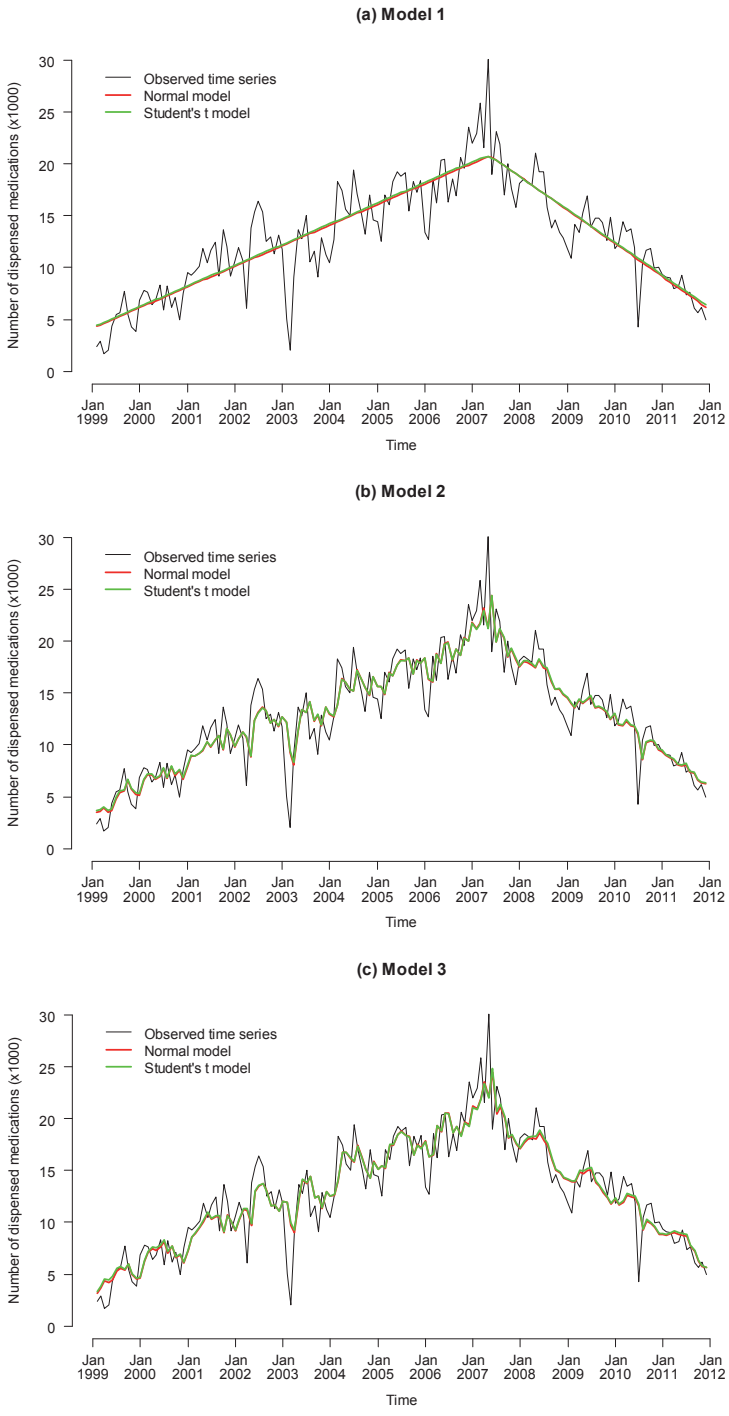

Figure 3: *Comparison between the observed time series and the time series estimated from the Models 1 to 3, with residuals following a normal distribution and a Student's t-distribution with υ degrees of freedom.*

parameters of the model can be harmed from this lack of independence for the residuals. Results from the fit of the Models 2 and 3, considering autoregressive terms of order 1, are also shown in Tables 2 and 3 and visualized in the Figure 3. Considering the fit with residuals that follow a normal distribution, the change-point was now estimated by $t = 102.3$ (Table 2), corresponding to the month of July, 2007, with a 95% credible interval ranging from May, 2007, to November, 2007. Autocorrelation plots (not shown) for the residuals from Models 2 and 3 did not evidence significant serial correlation between successive values of ε_t, indicating a good fit of the model to the data. The central and lower panels of the Figure 3 show the predicted values obtained from Models 2 and 3, respectively. In both models, the estimate for the variance σ_1^2 was greater than the estimate for σ_2^2, suggesting a higher dispersion of the number of dispensed medications before the change-point.

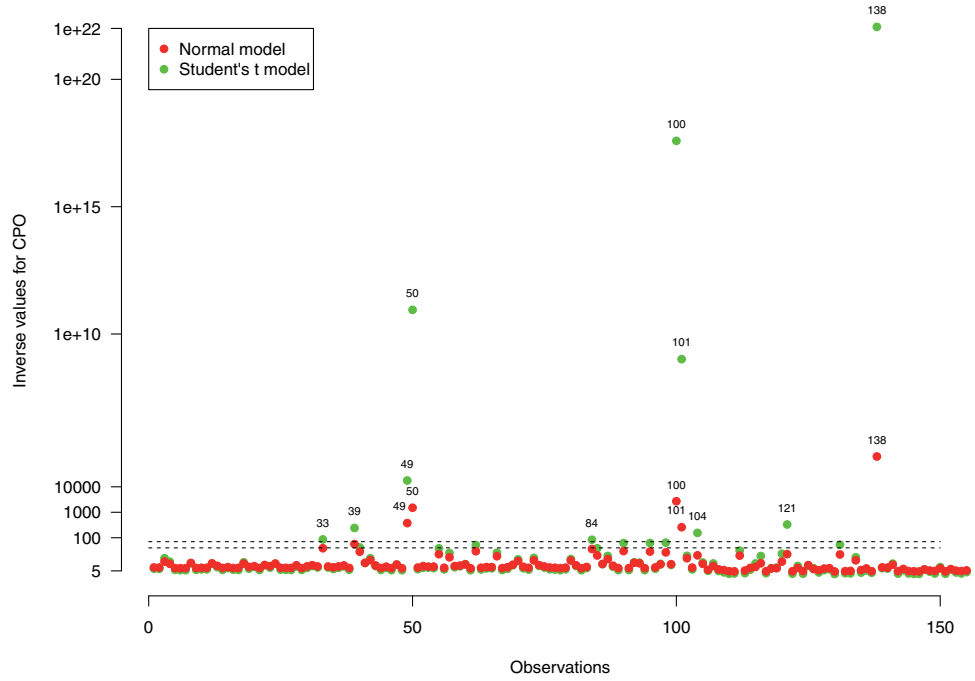

Figure 4: *Comparison between inverse values for CPO obtained from the Model 3 considering residuals following a normal distribution and a Student's t-distribution with υ degrees of freedom. The horizontal dashed lines pass through the values 40 and 70, identifying possible outliers and extreme values, respectively.*

Examination of a plot of inverse values for CPO values can identify possible outliers in the model fitting, thus allowing for comparisons between models. Considering the results from the Model 3, the graph in Figure 4 corresponds to the plot of inverse values for CPO, where the two horizontal dashed lines in the figure pass through the values 40 and 70, identifying possible outliers and extreme values, respectively (see Subsection 2.4). This graph compares the inverse values for CPO obtained from the Model 3 con-

sidering residuals following a normal distribution and a Student's t-distribution with υ degrees of freedom. We can note that the number of the extreme values is greater when considering the model with residuals following a Student's t-distribution, thus reinforcing that the model with errors following a normal distribution is the model that best fits to the data.

We also fitted alternative models that do not take into account the presence of a change-point, but consider the presence of autoregressive effects of high order. However, we observed that these models did not fit well to the data. For example, for models with residuals following a normal distribution and autoregressive effects of orders 4 and 5, we obtained LPML values given by -357.9 and -354.9, respectively, and SSR values given by 891.2 and 866.4, respectively. In addition, for models with residuals following a Student's t-distribution and autoregressive effects of orders 4 and 5, we obtained LPML values given by -436.7 and -435.4, respectively, and SSR values given by 892.6 and 868.1, respectively.

Table 4: *Results from regression models that considers the monthly maximum and minimum absolute temperatures as independent variables.*

Parameter	Maximum absolute temperature (^oC)		Minimum absolute temperature (^oC)	
	Bayesian estimate	95% credible interval	Bayesian estimate	95% credible interval
α	18.41	(16.85 , 19.94)	18.1	(16.58 , 19.58)
β_1	0.110	(0.076 , 0.142)	0.103	(0.071 , 0.135)
β_2	-0.199	(-0.254 , -0.147)	-0.191	(-0.243 , -0.140)
θ	101.4	(100.0 , 106.0)	102.0	(100.0 , 107.0)
$\gamma_{1,1}$	0.384	(0.218 , 0.548)	0.403	(0.238 , 0.566)
$\gamma_{2,1}$	0.202	(0.005 , 0.413)	0.241	(0.042 , 0.447)
σ_1^2	6.13	(4.53 , 8.19)	6.34	(4.71 , 8.47)
σ_2^2	3.51	(2.29 , 5.37)	3.42	(2.22 , 5.29)
η_1	0.164	(-0.497 , 0.814)	0.453	(-0.044 , 0.944)
η_2	-0.413	(-0.985 , 0.164)	-0.433	(-1.42 , 0.551)
ψ_1	-0.195	(-0.470 , 0.084)	-0.025	(-0.196 , 0.145)
ψ_2	-0.132	(-0.436 , 0.174)	-0.030	(-0.207 , 0.147)
LPML		-353.8		-354.9
SSR		740.6		759.5

Tables 4 and 5 show the results from regression models (Model 4) in which monthly maximum and minimum absolute temperatures, average monthly temperature and monthly average precipitation are independent variables. These models assume that the residuals follow a normal distribution. For all these independent variables, we can observe that the 95% credible intervals for the parameters ψ_1 and ψ_2 include the value zero. This implies that we do not have evidence that these climatic variables are as-

Table 5: *Results from regression models that considers the monthly average temperature and precipitation as independent variables.*

Parameter	Monthly average temperature (^oC)		Precipitation (log mm)	
	Bayesian estimate	95% credible interval	Bayesian estimate	95% credible interval
α	18.14	(16.62 , 19.62)	18.1	(16.598 , 19.58)
β_1	0.104	(0.071 , 0.136)	0.103	(0.071 , 0.135)
β_2	−0.193	(−0.245 , −0.142)	−0.192	(−0.245 , −0.140)
θ	101.8	(100.0 , 107.0)	102.0	(100.0 , 107.0)
$\gamma_{1,1}$	0.401	(0.236 , 0.563)	0.403	(0.239 , 0.566)
$\gamma_{2,1}$	0.235	(0.038 , 0.438)	0.234	(0.032 , 0.442)
σ_1^2	6.26	(4.62 , 8.41)	6.26	(4.66 , 8.33)
σ_2^2	3.41	(2.22 , 5.28)	3.50	(2.26 , 5.48)
η_1	0.321	(−0.223 , 0.863)	0.462	(−0.035 , 0.957)
η_2	−0.142	(−1.053 , 0.758)	−0.718	(−1.391 , −0.035)
ψ_1	−0.204	(−0.551 , 0.146)	0.061	(−0.164 , 0.287)
ψ_2	−0.164	(−0.517 , 0.191)	0.054	(−0.185 , 0.296)
LPML	−354.1		−354.8	
SSR	751.1		755.9	

sociated with the monthly number of dispensed medications. These results can be still observed even in similar models that not include the seasonal component S_t. Plots of the autocorrelation function (ACF) and the partial autocorrelation function (PACF) of the residuals from these models are shown in Appendix B (Figure 7). The ACF and PACF of residuals at different lag times were not significantly different from zero.

4. Discussion

Statistical methods of time series analysis are widely used in public health studies (Zeger, Irizarry and Peng, 2006; Jornet-Sanz et al., 2017). These methods are useful for detecting outbreaks, monitoring the occurrence of a disease at a regional level, analysing epidemiological surveillance data, describing the seasonality of infectious diseases, examining how climate change can affect the disease occurrence over time, and predicting future scenarios of an event of interest. In the present article, we introduced a Bayesian approach that can be used to estimate a change-point model with autoregressive terms. In the context of the monthly number of dispensed asthma medications, this model is useful to provide a better understanding of the corresponding time series, such as seasonal patterns, dependence on previous times and possible association with climatic variables.

Alternatively to the method presented here, a maximum likelihood estimate of the change-point θ can be obtained by using the profile likelihood approach. In this case, the profile likelihood $\ell_p(\theta)$ for θ is defined by maximizing the likelihood function with respect to all the other parameters in the model for a range of values for θ over which the profile likelihood is to be evaluated. Thus, the maximum likelihood estimate for the change-point is

$$\widehat{\theta}_{ML} = \arg_\theta \max \ell_p(\theta) = \arg_\theta \max \sum_{t=1}^{n} \ln f(y_t|\theta, \widehat{\boldsymbol{\xi}}_{ML}),$$

where $\widehat{\boldsymbol{\xi}}_{ML}$ is the vector of maximum likelihood estimates for the other parameters associated with the model. Although it is possible to implement a computer algorithm in order to find the maximum likelihood estimate for θ, presentation of this analysis is out of the scope of the present paper. We opted for the use of Bayesian methods, that make it easy to incorporate prior knowledge about the change-point value. In addition, Bayesian estimation is facilitated using the OpenBUGS software, that only requires the specification of the distribution for the data and the prior distributions for the parameters.

As previously mentioned, the present statistical model was developed using a time series of the dispensation of salbutamol sulfate tablets 2 mg. Currently, this presentation form of salbutamol sulfate is no longer considered the most appropriate because it is associated with a higher number of side effects when compared to other forms, such as the oral spray (Sociedade Brasileira de Pneumologia e Tisiologia, 2012). Salbutamol sulfate is also indicated for the treatment of other diseases such as chronic obstructive pulmonary disease (COPD), preferably via inhalation. This drug can still be used in some other situations, such as inhibition of uncomplicated premature labor in the last gestational trimester, in which oral administration is the preferable choice (Motazedian et al., 2010).

The graphs in Figure 2 shows that the behavior of the time series for the number of monthly dispensations of the salbutamol sulfate tablets of 2 mg from 1999 to 2011 is interpreted in terms of the presence of a change-point. The Brazilian National Drug Policy, introduced in October 30th 1998, established new guidelines for pharmaceutical care in the public health by defining, among other things, a list of essential medications according to the most common health problems reported in the population. Thereafter, and with the decentralization process of drugs distribution for the states and cities (Ordinance GM 176 of March 8th, 1999), it was possible to expand the supply of medications in public health network (Botega and Santos, 2007), which explains the increased number of dispensations of the medication at beginning of year 1999 (Figure 3). Fluctuations in the monthly number of medication dispensed are observed in the Figure 2), with some seasonality. It was hypothesised that local maximum points in the time series are coincident with colder and drier periods, when the airway infections and episodes of bronchospasm occur more frequently, creating a greater demand for the use of the medication in specific periods of the year (Thomazelli et al., 2007; Peterson et al., 2012).

However, the regression models used in this study do not show a significant association between climatic variables and the number of dispensed medication.

Figure 1 shows a great reduction in the dispensation of salbutamol by March 2003 and July 2010, suggesting a period of discontinuity in the supply of the medication. Despite the good results of the decentralization policy of the pharmaceutical care, the provision of essential medications and medicines in some special situations (drugs being part of specialized pharmaceutical care) depended largely on efforts of the Brazilian National Health System managers (Botega and Santos, 2007), which leads to unavailability of the medicament to the population. The reduction in March 2003 was followed by a further increase in the number of dispensations, which as observed until the month of May, 2007. In 2004, as part of the National Policy on Integral Health Care of People with Respiratory Diseases, the cities with primary healthcare services began receiving beclomethasone 250 mcg oral spray, beclomethasone 50 mcg nasal spray and salbutamol 100 mcg oral spray from the Brazilian Ministry of Health for treatment of both asthma and allergic rhinitis, and given that asthma and allergic rhinitis often co-exist in the same individual, the control of one of these diseases favors the control of another, thus contributing to the implementation of better health practices for asthma. At that moment, aminophylline 100mg tablets were being provided by National Health System and now they are no longer supplied, being replaced by salbutamol spray (Botega and Santos, 2007). Figure 2 shows a further reduction in the number of dispensations of salbutamol sulfate from 2007 to the end of 2011, characterizing a change-point that probably reflects the improvement of healthcare provided to patients with asthma when the new medications were introduced.

As a final consideration, the article provides suggestions for future investigations:

(a) Possible extensions of the model in order to accommodate more than one change-point should be considered in future research works.
(b) In the proposed model, we assumed constant variances before and after the change-point. Future works can assume the effect of covariates on these variances, thus improving the fit of the proposed model.
(c) The actual numbers for asthma medication are huge, as discussed in this paper, and therefore the model assumptions are very reasonable. Extensions of the proposed model for low count data are essential for the analysis of a large broad of other epidemiological time series.
(d) By considering the data shown in Table 1, the change-point can be seen in the central part of the time series. Studies with simulated data can be useful to verify the performance of the proposed model in estimating the change-point when the period after change is short (or say, when there are few observations after the change).

Appendix A

The OpenBugs code used to specify the statistical model in its general form and with residuals following a normal distribution is given below. Observations of the independent variable are denoted by `x[t]`. In addition, `cp` denotes the change-point value and `N` is the length of the time series.

```
model
{
for(t in 1:N) {
y[t] ~ dnorm(mu[t], tau[J[t]])
mu[t] <- alpha + beta[J[t]]* (t-cp)
 + gama[J[t]]* (w[t] - mean(w[])) + St[t]
 + phi[J[t]]*(x[t] - mean(x[]))
k[t] <- step(t - cp - 0.5)
J[t] <- 1 + k[t]
punif[t] <- 1/N
St[t] <- eta[1]*sin(2*pi*t/12) + eta[2]*cos(2*pi*t/12)
# Likelihood function
L[t] <- 1/sqrt(2*pi*(pow(sigma[1],1-k[t])
 * pow(sigma[2],k[t])))
 * exp(-(y[t]-mu[t])*(y[t]-mu[t])
 /(2*(pow(sigma[1],1-k[t]) * pow(sigma[2],k[t]))))
# Inverse values for CPO
PO[t] <- 1/L[t]
}
for(i in 2:N) { w[i] <- y[i-1] }
w[1] <- y[1]
pi <- 3.14159265359
# Prior distributions
prec <- 1.0E-6
alpha ~ dnorm(0.0, prec)
cp ~ dcat(punif[])
for(j in 1:2) {
 beta[j] ~ dnorm(0.0, prec)
 eta[j] ~ dnorm(0.0, prec)
 gama[j] ~ dnorm(0.0, prec)
 phi[j] ~ dnorm(0.0, prec)
 tau[j] ~ dgamma(0.1,0.1)
 sigma[j] <- 1/tau[j]
}}
```

Appendix B

Figures 5 and 6 show autocorrelation functions (ACF) and partial autocorrelation functions (PACF) of the residuals of the Models 1, 2 and 3 based on the normal distribution (Figure 5) and Student's t-distribution (Figure 6). Dashed horizontal lines correspond to the significance boundaries for the non-zero terms. By comparing the plots in Figures 5 and 6, we can observe that the ACF and PACF functions from the models with residuals based on normal and Student's t-distributions are quite close one another. The Figures show that there was no significant autocorrelation between residuals at different lag times for the Models 2 and 3.

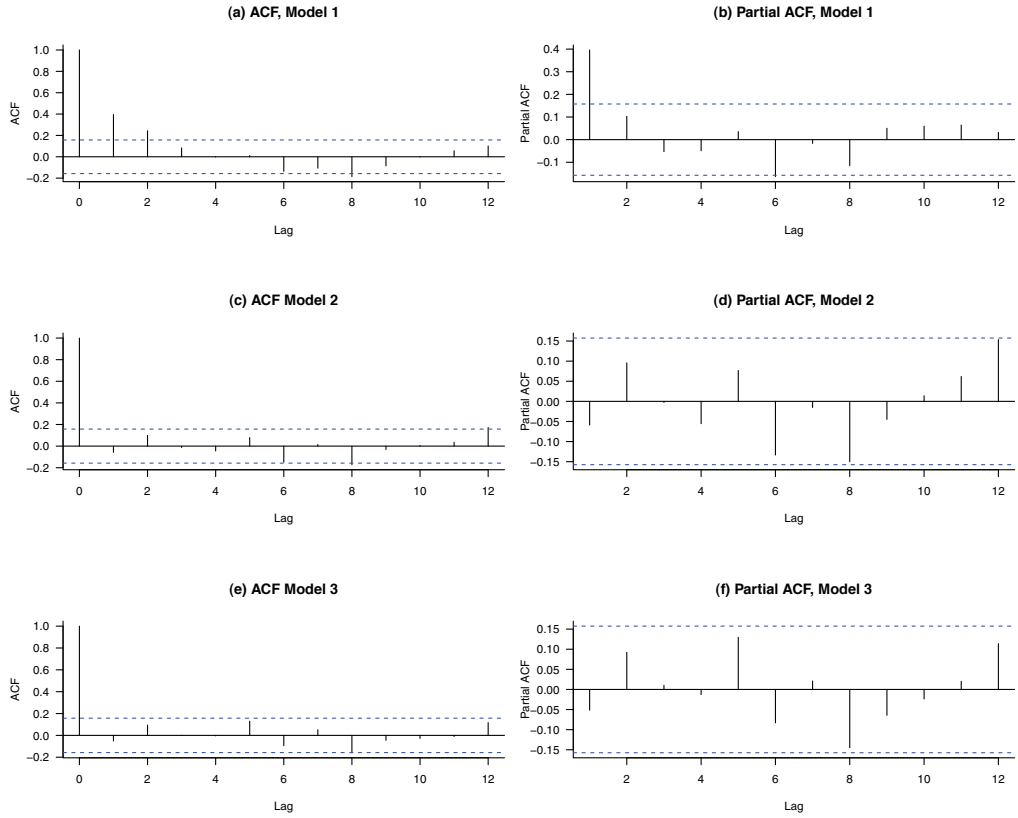

Figure 5: *Autocorrelation function (ACF) and partial ACF (PACF) plots for the residuals considering the Models 1, 2 and 3 based on the normal distribution. In each plot, two horizontal dashed lines denote two standard error limits of sample autocorrelation function.*

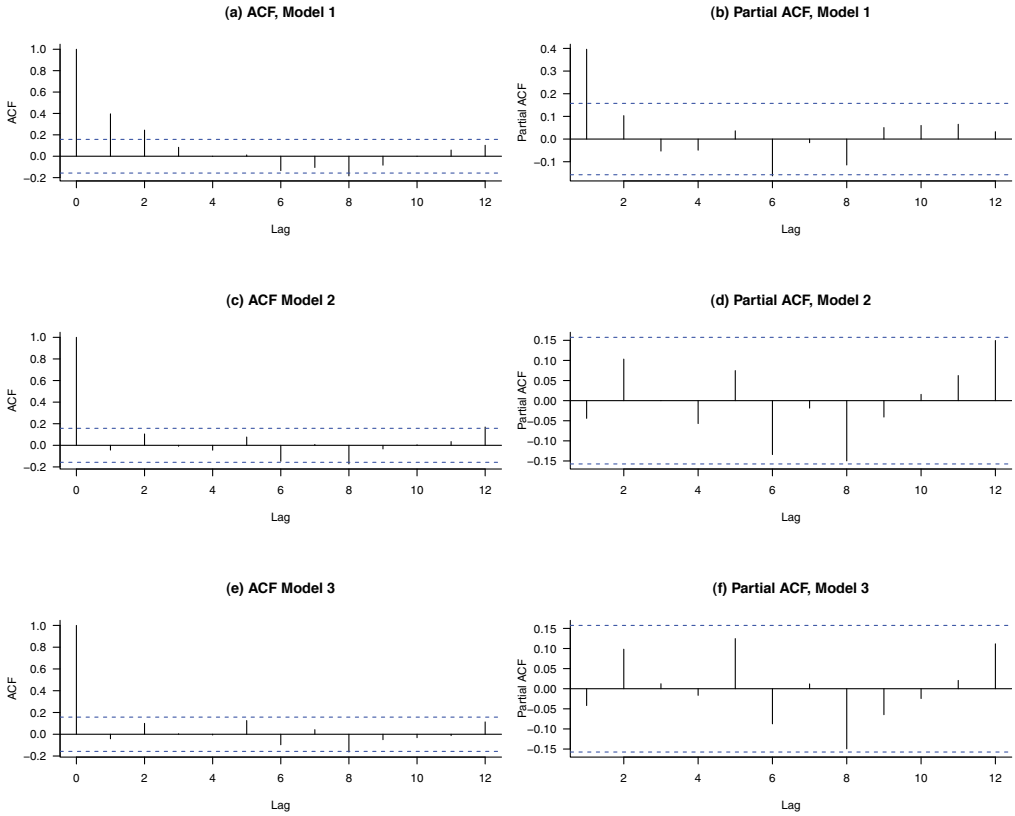

Figure 6: *Autocorrelation function (ACF) and partial ACF (PACF) plots for the residuals considering the Models 1, 2 and 3 based on the Student's t-distribution. In each plot, two horizontal dashed lines denote two standard error limits of sample autocorrelation function.*

Figure 7 shows ACF and PACF of the residuals of the Model 4, based on the normal distribution and including the climatic variables as independent variables. The plots show that there was no significant autocorrelation between residuals at different lag times.

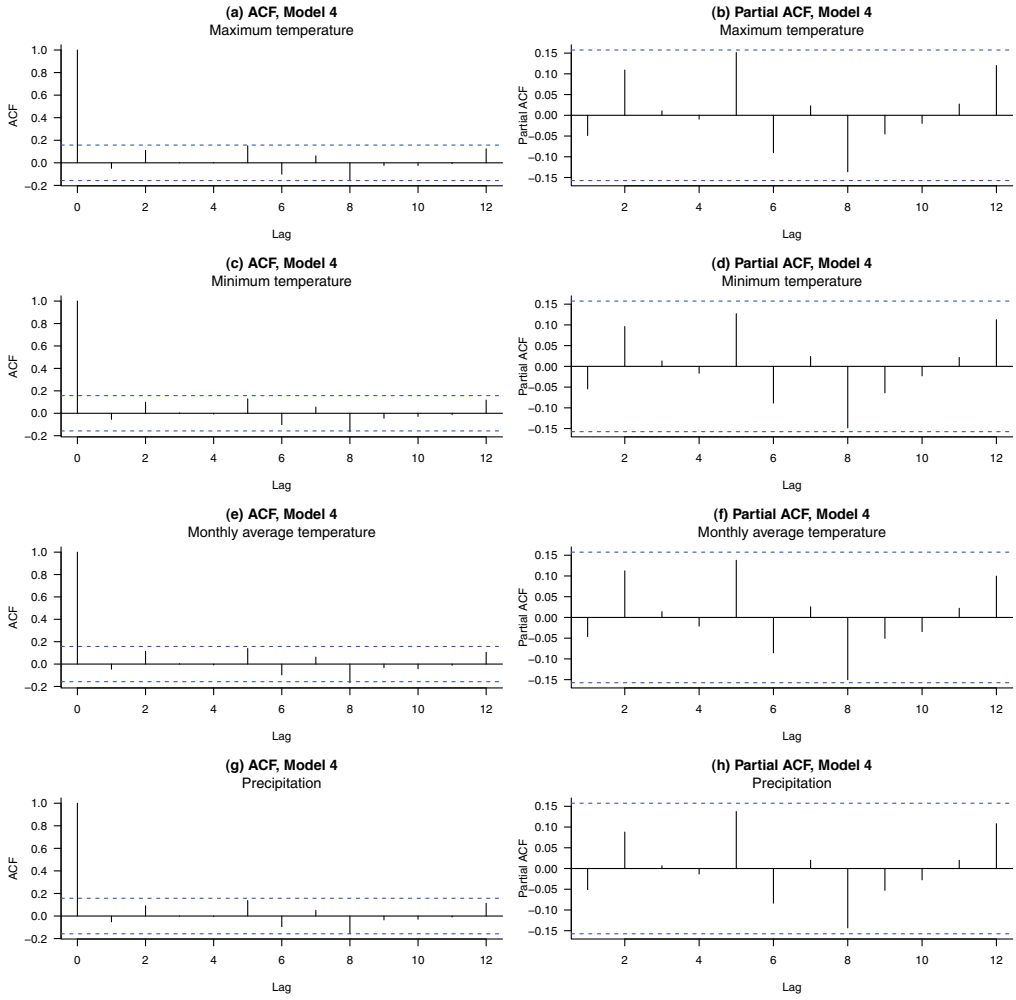

Figure 7: *Autocorrelation function (ACF) and partial ACF (PACF) plots for the residuals considering the Model 4 based on the normal distribution and the climatic variables included as independent variables. In each plot, two horizontal dashed lines denote two standard error limits of sample autocorrelation function.*

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